Atty. Dkt. No. 053466-0201

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant: Tadmitsu KISHIMOTO et al.

Title: METHODS OF TREATING DISEASES CAUSED BY INTERLEUKIN-6 (IL-6) PRODUCTION

Appl. No.: 08/817,507

Filing Date: April 17, 1997

Examiner: Karen A. CANELLA

Art Unit: 1642

BRIEF ON APPEAL

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

This Appeal Brief is in furtherance of the Notice of Appeal filed in this case on March 10, 2003. The brief is transmitted in triplicate, in conformance with 37 CFR §1.192(a). The fees required under 37 C.F.R. §1.17(f) and for the petition for extension of time are included in the attached check. Any fee deficiency or overpayment may be charged or credited to our Deposit Account 19-0741.

This is an appeal from the Office Action dated September 10, 2002 ("the Final Rejection"), finally rejecting claims 15 and 24-28 under 35 U.S.C. § 103(a). On June 19, 2003, Applicants submitted a Reply Under 37 C.F.R. §1.16 to the Examiner. The Examiner responded with an Advisory Action ("the Advisory Action") mailed on August 11, 2003, maintaining the final rejection of claims 15 and 24-28 for the reasons of record.

REAL PARTY IN INTEREST

The real party of interest is Tadamitsu Kishimoto and Chugai Seiyaku Kabushiki Kaisha.

RELATED APPEALS AND INTERFERENCES

It is submitted that there are no other appeals or interferences known to Appellants or Appellants' legal representative that will directly affect or be directly affected by, or have a bearing on, the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 15 and 24-28 are pending in the captioned application. Claims 15 and 24-29 stand rejected in the Final Rejection and the Advisory Action. A copy of claims 15 and 24-29, at issue in this appeal, are presented in APPENDIX I.

STATUS OF AMENDMENTS

The last amendment, filed August 28, 2001, in response to the non-final Office Action of February 28, 2001, has been acknowledged and entered. Subsequent to the issuance of the Final Rejection (Paper No. 35), no amendments have been filed.

SUMMARY OF INVENTION

The invention pertains to methods of treating a patient suffering from an elevated blood level of ionized calcium accompanied by cachexia caused by interleukin-6 (IL-6) production, comprising administering an antibody to an IL-6 receptor. *See* specification, page 1, lines 6-10 and 26-28; page 25, line 36 – page 26, line 3; and page 26, line 35 – page 27, line 2. Independent claim 15, and therefore dependent claims 24-28, recite, *inter alia*, the phrase "administering . . . an antibody to an IL-6 receptor . . . to suppress elevation of blood levels of ionized calcium."

ISSUES

Did the Examiner improperly rely upon teachings disclosed for the first time in Applicants' specification, not taught or suggested in the prior art, to assert obviousness of certain claimed elements by inherency?

Does Emilie *et al.* (Blood, 1994, Vol. 84, pp. 2472-2479) in view of Sato *et al.* (Cancer Research, 1993, Vol. 53, pp. 851-856) substantiate a *prima facie* case of obviousness under 35 U.S.C. § 103(a) with respect to appealed claims 15 and 24-28?

GROUPING OF CLAIMS

Claims 15 and 24-28 stand or fall together.

SUMMARY OF THE ARGUMENT

The Examiner has not established a *prima facie* showing of obviousness under 35 U.S.C. § 103(a). First, the Examiner erred in applied the doctrine of inherency in a way contrary to controlling precedent by concluding that the prior art rendered certain elements of the claimed invention inherently obvious based on teachings in Applicants' own specification. Second, the Examiner provided no evidence that one of skill in the art at the time of filing would have recognized that certain elements of the claimed invention were necessarily present in the prior art. Third, neither Emilie *et al.* nor Sato *et al.*, either alone or in combination, teach or suggest all elements of the claimed invention. For example, neither reference teaches or suggests "administering . . . an antibody to an IL-6 receptor . . . to suppress elevation of blood levels of ionized calcium," as recited in the claims. Thus, the pending obviousness rejection is erroneous and should be reversed.

ARGUMENT

Claim are not be rendered inherently obvious based on teachings in Applicant's own specification

In the Final Rejection of claims 15 and 25-28 under 35 U.S.C. §103(a), the Examiner suggests that at least one recited element in the claims (e.g., "to suppress elevation of blood levels of ionized calcium") is rendered obvious by the teachings of Emilie *et al.* and Sato *et*

al., despite the fact that neither reference suggests a method of using an anti-IL-6 receptor antibody to reduce blood levels of ionized calcium in cachexia patients. In the Final Rejection, the Examiner bases this contention on M.P.E.P. 2141.02, reciting the passage that states: "In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question . . . but also to those properties of the subject matter which are *inherent in the subject matter and are disclosed in the specification* . . . ." (Emphasis in Examiner's Final Rejection).

Likewise, in the Advisory Action, the Examiner again relies on M.P.E.P. 2141.02. Advisory Action, page 3, lines 7-11. The Examiner notes Applicant's argument "that none of the prior art references qualifies as an inherent disclosure of the suppression of elevated levels [of] ionized calcium in the blood." *Id.* at page 2, lines 18-19 (1st sentence, 3rd ¶). In response, however, the Examiner simply states: "The binding of the PM-1 antibody [disclosed in Sato et al.] to the IL-6 receptor of the prior art *will have the same effect in a person suffering from cachexia as the instant claimed method, which specifies that reduction of ionized calcium levels will occur*. Thus the reduction in ionized calcium levels is inherent . . . ." *Id.* at page 4, lines 6-9 (emphasis added). In other words, the Examiner acknowledges that Applicant's own disclosure, not the prior art, teaches that reduction of ionized calcium blood levels occurs upon administration of antibodies that bind IL-6 receptors.

Based on M.P.E.P. 2141.02, the Examiner appears to suggest that it is appropriate to find a recited element inherently obvious based on a teaching in the specification/claims, regardless of what the prior art teaches. To the contrary, M.P.E.P. 2141.02 explains that: (1) the Examiner must consider the invention "as a whole"; and (2) the invention as a whole includes not only the subject matter literally recited in claims, but also the "properties of the subject matter which are inherent in the subject matter and are disclosed in the specification." In other words, the passage explains what is meant by the invention "as a whole," which is what the Examiner must consider when determining whether the claims are obvious in light of the prior art.

M.P.E.P. 2141.02 does not suggest, however, that a claim may be rendered obvious by teachings in the specification disclosing a recited (or inherent) claimed feature when that feature is not taught or suggested anywhere in the prior art. In fact, M.P.E.P. 2141.02 clearly explains that "[o]bviousness cannot be predicated on what is not known at the time an

invention is made, even if the inherency of a certain feature is later established." *See* M.P.E.P. Rev. 1 Feb. 2003, page 2100-122, ¶ spanning 1st and 2nd cols.

Moreover, Applicants' own discovery of a particular property may not be used as evidence against them in determining whether the prior art makes a case of prima facie obviousness. *In re Dillon*, 919 F.2d 688, 718-19 (Fed. Cir. 1990) (stating that applicant's own disclosures can not be used to support a rejection of the claims "absent some admission that matter disclosed in the specification is in the prior art") (citing *In re Wertheim*, 541 F.2d 257, 269 (C.C.P.A. 1976).

Thus, the Examiner erred by suggesting that Emilie *et al.* and Sato *et al.* render the claimed invention obvious "because the *specification* discloses that said elevated level of calcium is due to the production of IL-6." Final Response, pages 2-3 (emphasis added). Likewise, the Examiner erred by suggesting that the two references rendered the invention obvious because the "*instant claimed invention* [] specifies that reduction of ionized calcium levels will occur" upon administration of an antibody to the IL-6 receptor. Advisory Action, page 4, lines 6-8 (emphasis added).

Examiner provided no evidence that one of skill in the art would have recognized that certain elements of the claimed invention were necessarily present in the prior art

In establishing a prima facie case under § 103, the Examiner must marshal disclosures, from a reference or combination of references, that teach or suggest all of the elements of the claims. The Examiner has suggested that certain recited elements in the claims (e.g., "to suppress elevation of blood levels of ionized calcium") are rendered inherently obvious by the teachings of Emilie *et al.* and Sato *et al.* The Examiner necessarily relies upon the doctrine of inherency because neither reference suggests a method of using an anti-IL-6 receptor antibody to reduce blood levels of ionized calcium in cachexia patients.

When asserting in an obviousness rejection that an element is inherently present in the prior art, the burden is on the Examiner to provide evidence that "the missing descriptive matter is *necessarily* present in the thing described in the [prior art] reference, and *that it*

would be so recognized by persons of ordinary skill." *In re Robinson* 169 F.3d 743, 745 (Fed. Cir. 1999) (emphasis added); *see also* M.P.E.P. 2141.02 and 2112 [1]

The Examiner provides absolutely no evidence that one skilled in the art would have recognized at the time of filing that: (1) an antibody against the IL-6 receptor necessarily affects cachexia; (2) ionized calcium is elevated in the blood of any cachexia animals/patients; and/or (3) administration of an antibody against the IL-6 receptor suppresses elevated blood levels of ionized calcium in cachexia patients. The present specification teaches the claimed invention for the first time. *See e.g.,* specification, page 25, line 36 – page 26, line 3; page 26, line 35 – page 27, line 2 (describing experiments with colon 26-induced cachexia models and occ-1-induced cachexia models); Figures 15 and 18 (comparing a tumor-bearing control group to a non-tumor-bearing control group).

Emilie et al. and/or Sato et al. do not teach or suggest all elements of the claimed invention

Because Emilie *et al.* and/or Sato *et al.* fail to teach or suggest each and every element in the claimed invention, these references cannot render Applicants' claimed methods obvious.

Emilie *et al.* discusses the administration of an antibody raised against IL-6, not an antibody against the IL-6 receptor. Thus, despite any findings by Emilie *et al.* using an anti-IL-6 antibody, there is no suggestion in the reference that administration of an antibody raised

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[1] Applicants note that there is a distinction between anticipation and obviousness when it comes to the doctrine of inherency. *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984). Recent Federal Circuit decisions have stated that anticipation by inherency does not require that a person of ordinary skill in the art at the time of filing would have recognized the inherent disclosure. *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1351 (Fed. Cir. 2002). The Examiner bases her rejections in the current application, however, on obviousness under §103, not anticipation under §102. Unlike anticipation, obviousness turns on what one of skill in the art would have understood at the time of filing. Consequently, obviousness by inherency requires that a person of skill in the art at the time of filing would have recognized the alleged inherent feature. M.P.E.P. 2141.02 (*see* page 2100-122, ¶ spanning 1st and 2nd cols., Rev. 1 Feb. 2003); *In re Rijckaert*, 9 F.3d, 1531, 1534 (Fed. Cir. 1993) ("'That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.' *In re Spormann*, 363 F.2d 444, 448, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966). Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection. *See In re Newell*, 891 F.2d 899, 901, 13 U.S.P.Q.2d 1248, 1250 (Fed. Cir.1989)."); *In re Dillon*, 919 F.2d 688, 718 (Fed. Cir. 1990) ("Arguments based on 'inherent' properties can not stand when there is no supporting teaching in the prior art. Inherency and obviousness are distinct concepts").

against an IL-6 receptor would necessarily affect cachexia in patients. Emilie *et al.* states that "[i]t has been shown that IL-6 itself is a potent inducer of cachexia." 84(8) Blood 2472, 2477, 2nd col., lines 9-10 (1994). Consequently, one of skill in the art would have thought it possible that IL-6 exerted its effect of inducing cachexia based on an as-yet undiscovered mechanism that did not require binding to IL-6 receptors. Nothing in Emilie *et al.* (or any other cited reference) suggests that antibodies against an IL-6 receptor would necessarily act the same way as an anti-IL-6 antibody with regard to cachexia.

Moreover, Emilie *et al.* does not teach or suggest that elevated blood levels of ionized calcium (i.e., hypercalcemia) accompanies cachexia. Similarly, this reference does not disclose or suggest that hypercalcemia should be controlled in cachexia patients, or that it can be controlled by administration of an anti-IL-6 receptor antibody. In fact, Emilie *et al.* fails to mention hypercalcemia at all, much less suggest any relation between hypercalcemia and IL-6 or its receptor.

Furthermore, even assuming (as is not the case here) that Emilie *et al.* disclosed a suppression of hypercalcemia in cachexia patients upon administration of the anti-IL-6 antibody, that disclosure would not necessarily suggest the same result with an anti-IL-6 receptor antibody. To put it another way, even assuming that an anti-IL-6 antibody blocked a particular IL-6-induced cell signal transduction event, that fact would not necessarily indicate that an anti-IL-6 receptor antibody would block the same event. Those skilled in the art knew that blood contained soluble IL-6 receptors, in addition to IL-6 receptors present on cell membranes. Skilled artisans therefore understood that anti-IL-6 receptor antibodies might bind to soluble IL-6 receptors, rather than cell surface IL-6 receptors. Consequently, a skilled artisan would not have recognized that an anti-IL-6 receptor antibody would *necessarily* block any particular IL-6-induced signal transduction event in cells.

In addition, skilled artisans also knew that blood contained a larger amount of IL-6 receptor compared to that of IL-6 (pg/ml level). Thus, skilled artisans would have believed that the amount of anti-IL-6 receptor antibody necessary to block IL-6-induced signal transduction would have been greater than that of the anti-IL-6 antibody. Thus, prior to the present invention, one of ordinary skill would not have necessarily expected to see similar results with an anti-IL-6 receptor antibody as with an anti-IL-6 antibody.

Like the Emilie reference, Sato *et al.* does not teach or suggest that hypercalcemia accompanies cachexia. Rather, the Sato reference simply shows that an IL-6 receptor antibody inhibits growth of human multiple myeloma cell lines *in vitro*. Thus, this reference does not demonstrate any results *in vivo* or otherwise address concerns of those skilled in the art regarding the administration of antibodies against IL-6 receptor *in vivo* (e.g., that blood contains soluble IL-6 receptors, and contains many more IL-6 receptors than IL-6—*see* above discussion). Likewise, the Sato reference does not disclose or suggest that hypercalcemia should be controlled in cachexia patients, or that hypercalcemia can be controlled by administration of an anti-IL-6 receptor antibody. In fact, like Emilie *et al.*, Sato *et al.* fails to mention cachexia or hypercalcemia at all, much less suggest any relation between hypercalcemia and IL-6 or its receptor.

Thus, Sato *et al.* fails to cure the deficiencies of Emilie *et al.* The claimed methods for using an anti-IL-6 receptor antibody to suppress elevated blood levels of ionized calcium in cachexia patients were unknown to those skilled in the art prior to Applicants' invention. Neither Emilie *et al.* or Sato *et al.*, alone or in combination, teach or suggest methods for suppressing hypercalcemia in cachexia patients by administering an anti-IL-6 receptor antibody. Neither reference mentions hypercalcemia at all, or suggests any relation between hypercalcemia and cachexia or IL-6 or its receptor.

In summary, the Examiner provides no objective evidence that certain claimed elements (alleged by the Examiner to be "inherent" in the prior art) are *necessarily* present in the experiments described in Emilie *et al.* and Sato *et al.*, or that these claimed elements *would have been recognized by persons of ordinary skill.* Applicants' specification discloses for the first time that: (1) administration of an antibody raised against the IL-6 receptor affects cachexia; (2) elevated levels of calcium correlates with cachexia; and (3) administration of an antibody raised against the IL-6 receptor suppresses the elevation of blood levels of ionized calcium accompanied by cachexia. The prior art cited by the Examiner did not teach, suggest or otherwise motivate those skilled in the art to practice Appellants' claimed methods with a reasonable expectation of success.

The Examiner has failed to establish a *prima facie* showing of obviousness. Emilie *et al.* and/or Sato *et al.* do not, expressly or inherently, teach or suggest all elements of the claimed invention.

CONCLUSION

Based upon the foregoing, Appellants respectfully request that the Board reverse the Examiner's rejection and remand this application for issuance.

Respectfully submitted,

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

APPENDIX I

15. A method of treating a patient suffering from an elevated blood level of ionized calcium accompanied by cachexia caused by interleukin-6 (IL-6) production comprising administering to said patient a therapeutically effective amount of an antibody to an IL-6 receptor in a pharmaceutically acceptable carrier to suppress elevation of blood level of ionized calcium and wherein the therapeutically effective amount blocks signal transduction by IL-6 and inhibits the binding of IL-6 to the IL-6 receptor.

24. The method according to claim 15, wherein said antibody is a monoclonal antibody.

25. The method according to claim 24, wherein said monoclonal antibody is the PM-1 antibody produced by hybridoma PM-1, accession number FERM BP-2998.

26. The method according to claim 24, wherein said monoclonal antibody is a chimeric antibody comprising the variable immunoglobulin heavy and light chains from a murine monoclonal antibody to an IL-6 receptor and the constant immunoglobulin heavy and light chains from a human monoclonal antibody.

27. The method according to claim 24, wherein said monoclonal antibody is a humanized murine monoclonal antibody to an IL-6 receptor.

28. The method according to claim 27, wherein said humanized murine monoclonal antibody to an IL-6 receptor is a humanized PM-1 antibody, wherein the PM-1 antibody prior to humanization is produced by hybridoma PM-1, accession number FERM BP-2998.